REMARKS

Status of Claims and Amendment

Claims 17, 24, and 26 have been amended. Claims 1-16, 18, 19, 22, 23, and 25 have been canceled. Claims 17, 20, 21 and 24-26 are pending in the application. Claims 17, 20-22 and 24-26 are rejected.

Claims 17, 24, and 26 have been amended to incorporate the limitations of claims 22 and 25, i.e., to even further clarify that "the p10 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NO:5, 6, 7 or 8."

No new matter is added.

Claim of Priority

Applicants thank the Examiner for acknowledgement of Applicants' claim of priority to Japanese Application No. 2003-078898 filed March 20, 2003, Japanese Application No. 2003-086490 filed March 26, 2003, and Japanese Application No. 2003-086491 filed March 26, 2003, as well as receipt of the certified copies of the priority documents.

Drawings

Applicants thank the Examiner for indicating acceptance of the drawings filed March 22, 2004.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing the rejections to claims 17, 20-22 and 24-26 under 35 U.S.C. § 112, first paragraph, for lack of written description and lack of enablement.

Response To Claim Rejections Under 35 U.S.C. § 103

Claims 17, 20-22 and 24-26 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Yamaguchi et al. *(Ann. Clin. Biochem.* 2001, 38:348-355, "Yamaguchi"), in view of Watanabe et at. (*J. Vet. Med. Sci.*, 2000, 62(7):775-778, "Watanabe"), as evidenced by Planz et at. (*Journal of Virology*, 1999, 73:6251-6256, "Planz") and further in view of Hatalski et at. (*Journal of Virology*, February 1995, 69(2):741-747, "Hatalski"), and Carbone, K.M. (*Clin. Micro. Rev.*, 2001, 14(3):513-527, "Carbone"), for the reasons of record.

Specifically, the Office Action asserts that Yamaguchi discloses a synthetic peptide-based electrochemiluminescence immunoassay (ECLIA) for anti-BDV p40 and p24 antibodies in rat and horse serum. The Office Action asserts that Yamaguchi teaches a p40 peptide that is identical to the claimed SEQ ID NO:3, and a p24 peptide that is identical to the claimed SEQ ID NO:1. The Office Action asserts that Yamaguchi discloses that ECLIA is used to detect rabbit anti-BDV p40 and p24 antiserum.

Watanabe is asserted for teaching that p10 antibodies are detected in sera of BDV-infected rats as early as anti-p40 and anti-p24 antibodies can be detected. The Office Action asserts that one of ordinary skill in the art would have been motivated to detect anti-p10 antibodies along with anti-p40 and anti-p24 for the purpose of increasing the sensitivity of the method of Yamaguchi. In this regard, the Office Action appears to assert that Watanabe suggests that antibodies to individual viral proteins and BDV-specific antigens are useful for establishing diagnostic methods.

Planz is asserted by the Office Action for teaching that the sequence of p10 includes SEQ ID NO:8.

Hatalski is asserted for testing the presence of IgG and IgM antibodies to recombinant and BDV proteins using electrochemiluminescence. The Office Action asserts that one of ordinary skill in the art would have been motivated to modify the method of Yamaguchi to test for the presence of IgM and IgG to detect infection as early as possible.

Carbone is asserted for teaching that the first serological evidence of virus infection is IgM antibody. The Office Action appears to assert that one of ordinary skill in the art would have had a reasonable expectation of success that testing for the presence of IgM and IgG would have worked by modifying the method of Yamaguchi.

In addition, the Office Action asserts that Applicants' arguments that Yamaguchi teaches an ECLIA assay that can only accurately assess BDV when combined with more specific tests such as Western blot (WB), are not persuasive because Yamaguchi teaches that the ECLIA disclosed in the paper is able to accurately identify antibodies to BDV in experimentally infected rats and horses (page 354, first column, third full paragraph). The Office Action asserts that although the ECLIA assay will not distinguish between an acute infection and a cleared infection, the ECLIA assay will determine whether or not an individual was ever infected by BDV. Accordingly, the Office Action asserts that Yamaguchi's statement regarding the combination of the ECLIA assay with WB or any other binding is merely a suggest of an improvement, and that Yamaguchi's assay is not limited to combinations of ECLIA and WB, but may be performed with the ECLIA assay alone. Thus, the Office Action asserts that Yamaguchi's ECLIA assay is sufficient to determine whether a subject has been infected with BDV.

With regard to Watanabe, the Office Action asserts that Applicants' arguments that Watanabe only discloses WB are not persuasive because although the Office Action acknowledges that Watanabe teaches WB analysis, Watanabe also discloses the use of an immunoassay to detect anti-pl0 antibodies (Figure 1). Watanabe is relied upon by the Office Action for teaching that anti-p10 antibodies (IgG) were detected in sera of BDV infected rats as early as anti-p40 and anti-p24 antibodies (abstract), and that these findings are useful for establishing diagnostic methods for BDV infection and for understanding its pathogenesis and replication (page 777, second column, last paragraph).

Thus, the Office Action concludes that it would have been obvious to include the detection of p10 in the method of Yamaguchi based upon the teachings of Watanabe, and one of ordinary skill in the art would have been motivated to also modify the method of Yamaguchi to test for the presence of IgM and IgG to detect infection as early as possible with an expectation of success based upon the teachings of Hatalski and Carbone

Initially, Applicants note that in order to establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 2143. Also, pursuant to M.P.E.P. § 2141.02, "determining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole." This means that "[i]n determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." Id.

With regard to Yamaguchi, Yamaguchi is directed to an electrochemiluminescence immunoassay (ECLIA) that specifically detects p40 and p24 antibodies because "antibodies to BDVp40 and p24 [are] expressed at high levels in the…brain and infected cells, [and] represent good markers with which to search for evidence of BDV infection in animal and human serum." (See Abstract and page 354, 1st column 1st paragraph of Discussion of Yamaguchi). Also, as acknowledged by the Office Action, Yamaguchi "is silent on the use of the antigen polypeptide of p10 (SEQ ID NO:8) and the aspect of testing for both IgM and IgG." (See page 4, last sentence of 1st full paragraph of Office Action).

Watanabe is relied upon by the Office Action in support of the contention that one of ordinary skill in the art would have been motivated to modify the ECLIA method of Yamaguchi to measure p10 because Watanabe teaches that p10 antibodies are detected in the sera of BDV-infected rats as early as anti-p40 and anti-p24 antibodies. (See Abstract of Watanabe). However, contrary to the Office Action's contentions, Watanabe which was published in 2000, one year before Yamaguchi, provided no such motivation to one of ordinary skill in the art because the ECLIA method of Yamaguchi is only directed to detection of p40 and 24 antibodies. Rather, as evidenced by the separate and combined teachings of Yamaguchi and Watanabe, one of ordinary skill in the art at the time the invention was made, would have only been motivated and guided by the teachings in the art to develop a diagnostic method to detect p40 and p24, and not the presently claimed method which consists essentially of assaying for both anti-BDV IgM antibody and anti-BDV IgG antibody which binds to p10 BDV synthetic antigen polypeptide and either p24 or p40 BDV synthetic antigen polypeptide, or the combination of p24 and 40 BDV synthetic antigen polypeptides, and assaying for both IgM and IgG.

In addition, as acknowledged by the Office Action, neither Yamaguchi nor Watanabe combined "disclose SEQ ID NO:8." (See page 4, 3rd full paragraph of Office Action). Nor does Yamaguchi or Watanabe teach or suggest the claimed SEQ ID NOs:5, 6, or 7. Planz adds nothing further to the teachings of Yamaguchi and Watanabe because Planz is solely asserted for teaching that the sequence of p10 includes SEQ ID NO:8.

Furthermore, the fact that the method of Yamaguchi may be modified to detect p10 antibodies does not render the claimed method obvious, especially if the references do not suggest the desirability of such a modification. M.P.E.P. § 2144.08. As disclosed by Watanabe, "abundant expression of p40 and p24 proteins in infected rat leads to function disorder of brain." (See page 776, 2nd column, lines 21-23 of Watanabe). Also, as discussed above, Yamaguchi discloses that "antibodies to BDVp40 and p24…[are] expressed at high levels in the…brain and infected cells, [and] represent good markers with which to search for evidence of BDV infection in animal and human serum." (See Abstract and page 354, 1st column 1st paragraph of Discussion of Yamaguchi). Nothing in Watanabe or Yamaguchi itself suggests the desirability of modifying the method of Yamaguchi to detect p10 antibodies.

Thus, there would have been no reason or motivation for one of ordinary skill in the art to combine Yamaguchi and Watanabe. The Office Action's conclusion of obviousness is solely based upon improper hindsight gleaned from Applicants' present disclosure.

Hatalski does not cure the deficiencies of Yamaguchi or Watanabe. Hatalski is asserted for testing the presence of IgG and IgM antibodies to recombinant and BDV proteins using electrochemiluminescence. Hatalski, which was published in 1995 before both Yamaguchi and Watanabe, provides no additional guidance to encourage or motivate one of ordinary skill in the

art to modify the ECLIA method of Yamaguchi to test for IgM and IgG. In fact, it is our understanding that Hatalski is directed to (1) determining the time course of neutralization activity and expression of antibodies to BDV infected rats, i.e., to detect antibodies to gp18 using an enzyme-linked immunosorbent assay (ELISA) because the appearance of the neutralizing antibodies correlates with immunological reactivity to gp18 in BDV infected rats (see Abstract and 1st paragraph at column 1, page 741 of Hatalski), and (2) identifying five MAbs[1] with BDV neutralizing activity, (see Table 2 at page 743 and page 744, 1st column, lines 3-11 of Hatalski). At most, one of ordinary skill in the art would have gleaned, based upon the disclosure in Hatalski, that the "role of neutralizing antibodies in Borna disease is less clear…[and that] [f]uture work will be directed toward determining whether passive administration of neutralizing antibodies or immunization with gp18 and other virion surface proteins can alter BDV pathogenesis." (See page 745, last paragraph of Hatalski).

Similarly, Carbone is a general review article published at the same time as Yamaguchi (July 2001), and merely provides a general overview of the Borna disease virus and the "technical difficulties in developing and validating a uniform test for diagnosis of BDV infection in humans." (See page 513, 1st and 2nd column of Carbone). Carbone adds nothing further to the teachings of Yamaguchi, Watanabe, and Hatalski because Carbone is solely asserted for teaching that the first serological evidence of virus infection is IgM antibody. As discussed at the paragraph bridging pages 6-7 of the specification, the fact that IgM is first raised upon viral infection was already commonly known in the art at the time the invention was made. However, as disclosed by Carbone, despite the knowledge in the art that IgM is first raised upon BDV viral

[1] The five MAbs are disclosed to represent three different isotypes, IgM, IgG2b, and IgG3.

infection, Carbone states that "we do not know how the detection of anti-BDV antibody relates to the presence or clearance of BDV in humans." (See page 516, 2nd column, lines 7-8 of Carbone). In fact, Carbone discloses that "most serological diagnostic tests for natural BDV infection are a single test for anti-BDV IgG from presumed convalescent-phase serum." (See page 516, 1st column, 1st sentence of 3rd full paragraph of Carbone). Accordingly, the only diagnostic test taught or suggested by the art and disclosed in Carbone is a single test for IgG.

In addition, although IgM was known in the art to be one of the antibodies that are first raised in response to an antigenic stimulus, the period of time required for class switching from IgM to IgG varied[2]. It would have been unpredictable for one of ordinary skill in the art at the time the invention was made, to include IgM in a diagnostic test because although these antibodies are among the first to appear, IgM disappeared rapidly due to a short half life to be gradually replaced with IgG. (See page 1, lines 12-15 of the specification).

Furthermore, despite the fact that Carbone acknowledges that, at the time the invention was made, "most serological diagnostic tests for natural BDV infection are a single test for anti-BDV IgG", Carbone appears to discourage or teach away from the use of such a single test because Carbone discloses that "[h]uman BDV infection can be successfully identified using a small number of carefully chosen subjects. It is likely that a series of tests for BDV infection status will perform more reliably than a single test; thus expectation of sensitive serological screening test (e.g., ELISA) followed by a confirmatory test (e.g., IB or RT-PCR) would be reasonable [emphasis added]." (See page 524, 1st column, lines 12-18 of Carbone). Such a

[2] For instance, from two months or longer, to one year or longer (see page 4, lines 9-11 of the specification).

teaching or suggestion away from using a single test is consistent with the disclosure of Yamaguchi because as acknowledged by the Office Action at the sentence bridging pages 5-6 of the Office Action, "Yamaguchi does indicate that the test would be even more accurate when combined with WB or another binding assay." Thus, there would have been no reasonable expectation by one of ordinary skill in the art that a single test such as that used in the presently claimed method would have successfully identified BDV infection. Rather, the state of the art at the time the invention was made strongly suggested performing a series of tests rather than a single test.

Pursuant to M.P.E.P. § 2143.02, obviousness requires at least some degree of predictability, and evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness.

Thus, for at least the reasons discussed above, neither Yamaguchi, Watanabe, Hatalski and Carbone teach or suggest the presently claimed

In addition to the above arguments, and because it is our understanding that none of the cited references discloses the presently claimed method for determining whether a subject has been infected with detecting Borna disease virus (BDV) infection in a subject wherein the p10 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NOs:5, 6, 7 or 8.

Reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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